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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HELLER EHRMAN WHITE & MCAULIFFE LLP
4350 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122-1246

EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,700	MADISON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-114* is/are pending in the application.

4a) Of the above claim(s) *20-49,56-58,62-64, and 73-114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-19,50-55,59-61 and 65-72* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *A, B & C* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse filed June 9, 2003, of Group 1, comprising claims 1-19, 50-55, 59-61 and 65-72 drawn to a MTSP7 protease or a catalytic domain thereof, conjugates and solid supports comprising same, and methods of use thereof in assays to identify compounds capable of modulating its proteolytic activity, is acknowledged. With respect to the division of the elected Group of product claims and Groups of claims describing further, alternative, methods of use of products of Group 1 in the restriction requirement mailed May 29, 2003, Applicant is advised as follows:

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier.** Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. §§101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. **See** "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. §121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Preliminary Amendment

Applicant's three Preliminary Amendments filed on May 24, June 17, and October 7, 2002, have been entered, the former providing the sequence listing in printed form, the

second amending the specification and claims 13, 23, 79, 109, 112 and 115, and the most recent amending claim 69.

Specification

The disclosure is objected to because of the following informalities: Page 158, line7 and 8, is unclear in its description of the preparation of the protease domain-encoding portion of the vector pPIC9KX in stating, "Nucleic acid encoding each the MTSP7 protease domain thereof was cloned". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 65-72 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

A claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility, but the instant application cannot identify any specific, substantial, utility for any modulator that might be identified by methods of claims 65-72 known to the inventors at the time the application was filed. It is agreed that the disclosed, native, MTSP7 protease is a product that has a specific and substantial utility because it can cleave a specific, artificial, tripeptide substrate, S-2366, and that this utility is present in at least one embodiment of each of product claims, i.e., the embodiment that is the disclosed, native, MTSP7 serine protease. But the specification teaches no specific utility for a potential modulator of the proteolytic activity of the disclosed, native, MTSP7 protease where it fails to disclose any *in vivo* proteolytic activity for the protease and provides no suggestion of any physiological or cellular function for the native protease. Where the public cannot use any modulator identified by a claimed assay to achieve a specific or substantial alteration of the unknown proteolytic activity of the disclosed, native, MTSP7 protease, the claimed assays to identify such modulators lack utility.

A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). There is no disclosure in the specification that suggests Applicant knew any specific utility for a modulator that might be identified by a claimed method at the time the application was filed that would permit its immediate use by the public in any specific or substantial fashion.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-72 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-7, 11-19, 50-55, 59-61 and 65-72 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not exemplifies or describe preparation of divergent species of MTSP7 proteases of claims 1-7 and 11-19 that have no particular function, nor does it exemplify or describe conjugates comprising such proteases of claims 50-55, solid supports or arrays of claims 59-61 comprising such proteases, nor the practice of assay methods of claims 65-72 utilizing such proteases, (1) where the claims lack a functional limitation requiring that such divergent polypeptides cleave at least the single disclosed substrate, S-2366, and (2) where the structure of a divergent polypeptide is defined by the statement at page 23, lines 10-26, of the specification with which claims 1-7, 11-19,

50-55, 59-61 and 65-72 must be construed. These structural limitations are inherent in lines 7-10 of claim 3, and in claims 12 and 13, describing coding polynucleotides "hybridizing under stringent conditions", where the particular clause of claim 3, a limitation maintained in the latter claims, permits a lesser, protease domain-encoding, polynucleotide to be the reference sequence in hybridization. The specification likewise fails to exemplify or describe the preparation of the subject matters of divergent species of MTSP7 protease muteins of claims 15-19 that have no particular function to the extent the structure of a divergent polypeptide is defined either by the 40% divergence of claim 15 or even the 10% divergence of claim 16, and further fails to exemplify or describe the preparation of conjugates of claims 50-55 comprising such polypeptides, arrays of claims 59-61 comprising such polypeptides, and the practice of assay methods of claims 65-72 utilizing such polypeptides. Whether the rejected claims reach generic polypeptides differing by as much as 40%, or as little as 10%, of the positions in the amino acid sequence of the integral protease having the 438-amino acid sequence set forth in SEQ ID NO:16 or its included catalytic domain having the 233-amino acid set forth in SEQ ID NO:18, neither the claims nor the specification describe where the differences occur nor what the differences should be and the specification does not otherwise disclose or suggest the nature or source of any generic proteins, "muteins", or splice variants embraced by the rejected claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of polypeptides diverging at as many as 175 amino acid positions, or as few as 44 amino acids, from the sequence of SEQ ID NO:16 or at as many as 93 amino acid positions, or as few as 23 amino acids, from the sequence of SEQ ID NO:18.

In addressing the issue of whether a disclosure of a molecular structure of one polypeptide of one biological species could adequately describe the molecular structure of a functionally similar molecule of another biological species, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, non-human and human proteases. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any undisclosed, generic, proteins that need not cleave the substrate S-2366 to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the generic proteases of claims 1-7 and 10-19, conjugates comprising such proteases of claims 50-55, and solid supports or arrays of claims 59-61 comprising such proteases, nor practice the assay methods of claims 65-72 utilizing such proteases.

Regardless of the holdings in *Fiers* and *Lilly*, discussed above, Example 14 of the USPTO's Written Description Guidelines establishes a "safe harbor" for the recitation of "at least 95% sequence identity" where a claim refers to the integral, unaltered amino acid sequence of a disclosed polypeptide, such as SEQ IDs NOs:16 and 18 herein and the claim further requires a disclosed function of the polypeptide, even though only a

single polypeptide species is disclosed in a specification. This "safe harbor" provides no shelter, however, from the following rejection for lack of enablement and cannot provide a haven from the prior art rejections stated hereinbelow.

Claims 1-7, 11-19, 50-55, 59-61, and 65-72 are also rejected under 35 U.S.C. § 112, first paragraph, because, while the specification is enabling for,

(i) a polypeptide capable of cleaving the artificial substrate S-2366 which may be a fusion polypeptide, that comprises the catalytic domain of the MTSP7 protease having the amino acid sequence set forth in SEQ ID NO:18,

(ii) a protease capable of cleaving the artificial substrate S-2366 consisting of the MTSP7 protease with the amino acid sequence set forth in SEQ ID NO:16 as well as its activation as a two-chain protease,

(iii) a protease capable of cleaving the artificial substrate S-2366 consisting of the MTSP7 protease catalytic domain with the amino acid sequence set forth in SEQ ID NO:18,

(v) a variant, or "mutein", of proteases of clauses (i)-(iii) wherein a free cysteine in the protease domain is replaced with another amino acid, such as serine, and,

(vi) conjugates comprising same, solid supports attached to same, and assay methods utilizing same,

is not enabling for any embodiment of a polypeptide comprising a MTSP7 protease, or catalytic domain thereof, wherein said protease or catalytic domain thereof has an amino acid sequence that diverges from the amino acid sequences of either of SEQ IDs NOs:16 or 18 at as many as 40%, or even 10%, of the amino acid positions of either amino acid sequence by amino acid substitutions, deletions and insertions, or combinations thereof, nor for conjugates comprising same, solid supports attached to same, and methods of screening for modulators of protease activity comprising same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

Claims 1-7 and 11-19 are rejected because they contemplate varying degrees of arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the amino acid sequences set forth in SEQ IDs NOs:18 and 16 of an integral MTSP7 protease and of its internal catalytic domain. Claims 50-55, 59-61, and 65-72 are included in this rejection because they depend from one of claims 1, 3, or 6 and incorporate the limitations of these claims describing varying degrees of arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the amino acid sequences set forth in SEQ IDs NOs:18 and 16 of an integral MTSP7 protease and

of its internal catalytic domain. The specification's teachings cannot support alterations producing a 10% amino acid divergence from the amino acid sequence of SEQ ID NO:18 permitted by claims 3 and 16, which are amino acid insertions, deletions, or substitutions anywhere, in any combination and in any pattern, in either the integral protease of SEQ ID NO:18 or the catalytic domain amino acid sequence set forth in SEQ ID NO:16. Indeed, neither the specification nor the prior art made of record herewith identify, taken together, 10% of the amino acids in the primary sequences of the human proteases matripase, PSA, and hepsin cited in the specification, that can be altered yet permit retention of the native proteolytic activity of the MTSP7 protease undisclosed in the specification. Applicant's specification cannot identify any 44 amino acid positions that might be altered, singly or jointly, in SEQ ID NO:16, nor identify as many as 23 amino acids that may be altered in the MTSP7 catalytic domain of SEQ ID NO:18, nor teach the nature of any alterations that may be made, that will permit resulting variants or "muteins" to function as a MTPS7 protease. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent protease enzymes and provide the public with a nucleotide sequence encoding an enzyme that retains its native function. The specification discloses no native substrate with which the artisan can determine whether an amino acid sequence alteration of SEQ ID NO:18 has resulted in a change in the native catalytic activity of the MTSP7 protease. That the absence of any disclosure of the native function of a MTSP7 protease defeats the enablement as to making of undisclosed variants and "muteins" is well demonstrated by the publication of Seffernick et al., 2001, **Journal of Biochemistry**, Vol. 183, pages 2405-2410, made of record with Applicant's Information Disclosure Statement of November 7, 2003, who teach that altering 9 amino acids in a sequence of 475 amino acids, a scant 2% of the native amino acid positions, in a deaminase will suffice to alter its substrate specificity and

require it to catalyze different reactions even though, page 2409, these alterations do not at all alter its tertiary structure and are spread throughout its primary structure. While Seffernick et al. were able to identify the alternative, native, substrates of both forms of the enzyme, the present application provides no teaching that permits artisans either to identify the cellular substrate(s) of the disclosed, native, MTSP7 or to determine whether or not any cellular substrate(s) of the disclosed MTSP7 can also be recognized and cleaved by a claimed MTSP7 variant.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard the Court of Appeals for the Federal Circuit adopted from its precursor, the CCPA, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with degree of unpredictability of factors supporting physiological action of small peptide hormone); **see also**, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the CCPA's standard in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

In *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994), the Federal Circuit considered whether definitional statements might

enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence and to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech,* 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

> a) the specification lacks adequate, specific, guidance for altering the amino acid sequences of MTSP7 proteases of SEQ IDs NOs:18 or 16 to the extent recited in the claims,
>
> b) the specification lacks working examples wherein MTSP7 proteases of any of SEQ IDs NOs:18 and 16 are altered to the extent recited in the claims,
>
> c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
>
> d) unpredictability exists in the art where no members of the class of human serine proteases comprising the MTSP7 amino acid sequence of SEQ ID NO:16 have had as many as fifteen amino acids specifically identified for concurrent modification.

Thus the scope of subject matters embraced by the phrase, "at least 90% identical thereto", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 11-19, 50-55, 59-61 and 65-72 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-7, 11-19, 50-55, 59-61 and 65-72 are indefinite due to the recitation, "comprising the protease domain of a type-II membrane type serine protease 7 (MTSP7) or a catalytically active portion thereof" at lines 2-3 of claim 1. This is because the term "type-II membrane type serine protease 7" in claim 1 may be construed according to a definition at page 23, lines 10-26, of the specification but the term is

otherwise a largely functional definition of intended subject matter unsupported by disclosure of any particular physiological or cellular function that might permit artisans and the public, seeking to ascertain the scope of the claims, to distinguish a MTSP7 protease from another, similar, membrane-bound serine proteases or functionally similar, soluble, serine proteases in the case of claims 4, 7 and 14. The only basis for a functional distinction among proteases embraced by the definition of a MTSP7 protease set forth in the specification is the ability, or inability, to cleave the artificial substrate S-2366 and the ambiguity arising from the lack of a critical structural definition of intended subject matters of claims affected by this aspect of the rejection is, in part, the basis for provisional double-patenting rejections that follow below, claims 2, 4-7, 11-19, 50-55, 59-61 and 65-72 are included in this rejection because they depend from claim, thus incorporate the ambiguous recitation at lines 2-3 of the claim, but fail to resolve the uncertainty as to the nature of the protease domain intended in claims 2, 4-7, 11-19, as well as the nature of the domain that may be joined to conjugates and solid supports of claims 50-55 and 59-61 and used in assays of claims 65-72 to identify modulators.

Claim 3 is independently indefinite in reciting, at lines 8-10, "that hybridizes along at least 70% of its full-length" . . . "to the sequence of nucleotides set forth as" . . . "or as", because the artisan and the public seeking to ascertain the scope of this clause of the claim, thus the claim as a whole, cannot determine the metes of bounds of encoding, hybridizing nucleic acids. This clause, and claim 3 as a whole, is further indefinite in reciting "under conditions of high stringency" because there are many such conditions and the claim fails to identify the specific hybridization and wash conditions that can define the degree of structural similarity that an encoding, hybridizing, nucleic acid must share. Claim 4 is independently indefinite in reciting, at line 2, "the MTSP7 portion of the polypeptide" because the recitation implies that a polypeptide of claim 1 must

comprise another, exterior, portion apart from its protease domain or "a catalytic portion thereof", which is yet another, interior, portion.

Claims 7 and 14 are independently indefinite in reciting, "consists essentially of the protease domain of MTSP7" because the artisan and the public attempting to ascertain the scope of these claims cannot determine, in view of the indications in the specification that a protease domain may comprise the amino acid sequence of SEQ ID NO:18, what is the essential portion of a MTSP7 protease domain of which the claimed polypeptide might consist. Claim 12 is independently indefinite in reciting the phrase, "that hybridizes along at least 70% of its full-length" . . . "to the sequence of nucleotides set forth as" . . . "or as", because the artisan and the public seeking to ascertain the scope of this clause of the claim, thus the claim as a whole, cannot determine the metes of bounds of encoding, hybridizing nucleic acids. This clause, and claim 12 as a whole, is further indefinite in reciting "under conditions of high stringency" because there are many such conditions and the claim fails to identify the specific hybridization and wash conditions that can define the degree of structural similarity that an encoding, hybridizing, nucleic acid must share.

Claims 15 and 17-19 are independently indefinite because their intended scope exceeds the scope of claim 3 from which they depend and claims 15-19 are further indefinite in referring back to proteases of claim 3 because recitations in these claims of the term "mutein" provide no further patentable distinction to a protease by comparison with the subject matters of claim 3, which expressly describes a genus of variant polypeptides in view of the definitions of the specification and the recitations of two of its clauses. Absent any designation in claims 3 or 15 of a specific, reference, amino acid sequence upon which a "mutein" of claims 15-19 might be based, or a description in claims 3 or 15 of the process of producing a mutein, the artisan and the public seeking to ascertain the scope of claims 15-19 cannot distinguish claimed "muteins" from those

generic MTSP7 variants of claim 3 which, for some indeterminable reason, are not "muteins". Claims 15-19 are further indefinite because claims 15 and 17, from which claims 16, 18, and 19 depend, recite, "has catalytic activity of at least 10 [or 50]% of the unmutated polypeptide" yet the specification discloses no catalytic activity that is particular to, and characteristic of, a MTSP7 protease that the artisan and the public, seeking to ascertain the scope of the claims, can identify with which to differentiate claimed "muteins" from other "muteins".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-7, 9-17, 50-55 and 65-72 are rejected under 35 U.S.C. §102(e)(1) as being anticipated by Plowman et al., WO 02/00860 and US 2002/0064856, made of record with Applicant's Information Disclosures of, respectively, May 16, and August 26, 2003.

To avoid redundancy, the disclosures of the published U.S. patent application of Plowman et al. are discussed herein rather than identical disclosures of the published International Application. Plowman et al. disclose, see SEQ ID NO:92 in Figure 2L and paragraph 0555, as well as Tables 1-4, the 425-amino acid sequence of a trypsin-related human serine protease designated SGPr426 linked to the human chromosomal locus 4q13. SEQ ID NO:92 of Plowman et al. comprises an amino acid sequence that is identical to that set forth in SEQ ID NO:18 herein, that is nearly identical to SEQ ID NO:16 herein between positions 1-171 inclusive, differing from SEQ ID NO:16 herein

only in the absence of the 13 amino acids between positions 172-184, inclusive, and a substitution of an alanine for the threonine at position 4 of SEQ ID NO:16 herein, and that is also completely identical to SEQ ID NO:16 herein between positions 185-438, inclusive. The disclosure of Plowman et al. thus meets limitations of claims 1, 3-5, and 9-17 herein and inherently anticipates the subject matter of claim 2 herein in disclosing, paragraphs 0235-0256, recombinant expression of their protease where Plowman et al. need not disclose a further protease or conditions that will activate their protease as a two-chain protease where the instant specification fails to disclose any further, activating, protease or conditions for activation of MTSP7 as a two-chain protease. Plowman et al. anticipate claims 6 and 7 as well because they disclose the location of the catalytic domain of their SGPr426 protease in the region bounded by amino acid positions 194 through 419, inclusive, in Table 3, and suggest the separate recombinant expression of its proteolytic domain, in paragraphs 0028, 0039, 0040, and 0240. Plowman et al. also anticipate the conjugates of claims 50-55 herein in disclosing, paragraph 0068, the preparation of fusion polypeptides directly linking their protease, which may be a separate, recombinantly-expressed proteolytic domain, to peptide and polypeptide targeting agents that permit the affinity isolation or purification of the protease. Plowman et al. additionally anticipate the assays of claims 65-70 herein in disclosing, paragraphs 0085-0100, the practice of assays utilizing their native protease or a fragment thereof consisting or its proteolytic domain to identify compounds such as those recited in claim 66 herein that modulate its activity as determined by changes in the amount of substrate cleaved in the presence of candidate modulatory compounds.

Claims 1, 3-7 and 11-17 are rejected under 35 U.S.C. §102(e)(1) as being anticipated by Alsobrook et al., US 2003/0170630, made of record herewith.

Alsobrook et al. disclose, SEQ ID NO:2, the 420-amino acid sequence of the human NOV1a protease that comprises the sequence of amino acids set forth in SEQ ID NO:18 herein and that is completely identical to SEQ ID NO:16 herein between

positions 160-438, inclusive, thus meets limitations of claims 1, 3-5, and 11-17, herein. Alsobrook et al. anticipate claims 6 and 7 as well because they disclose, paragraph 0071, the preparation of a NOV1a protease fragment having catalytic activity and retaining as little as 46% of its native amino acid sequence, thus including proteases retaining the native amino acid sequence region of SEQ ID NO:18 herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 59-61, 71 and 72 are rejected under 35 U.S.C. §103(a) as being unpatentable over Plowman et al. as applied to claims 1-7, 9-17, and 65-70 above, in view of Shen et al., U.S. 2003/0153014, made of record with Applicant's Information Disclosure Statement of November 7, 2003.

Disclosures of Plowman et al., discussed above, are taken as before. Shen et al., 2003/0153014 is available as prior art under 35 U.S.C. §102(3)(1) in view of the October 1999 filing date of the provisional application upon which the published application is based. Shen et al. generally teach, paragraphs 0010-0043, 0052, 0057, 0060-0067, 0073-0180, 0185-0189, and 0192-0210 and Figures 1 and 2, the preparation of polypeptide arrays comprising a solid support linked to a plurality of different polypeptides that are different members of a class having a common type of enzymatic activity, including proteases, from a common organ or tissue source, for the purpose of assaying the general and differential capacity of the enzymes to act on

members of a class of potential substrates, including polypeptide and peptide substrates. It would have been obvious to one of ordinary skill in the art to link the protease of Plowman et al., which comprises a catalytic domain identical to that set forth in both SEQ IDs NOs:16 and 18 herein, to a polypeptide array of Shen et al. together with other, related serine proteases from the same organ or tissue, in solid support arrays of claims 59-61 herein for the purpose of assaying the general and differential capacity of the proteases to act on members of a class of, at least, peptide substrates, as well as to conduct assays to identify modulatory compounds of claims 71 and 72 herein with such arrays. This is because Shen et al. teach that such arrays and such assays are important for the characterization of members of a class of enzymes and because of Plowman et al. teach that their serine protease should be used in assays, including drug screening assays that may be cell-free systems and in assays to identify compounds that modulate its protease ability.

Conclusion

Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583 until about January 21, 2004, and will be 571.272.0933 thereafter. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804 until about January 21, 2004, and at 571.272.0928 thereafter. The fax phone numbers for all communications for the organization where this application or proceeding is assigned is 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number remains 703.308.0196.

William W. Moore
December 11, 2003

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER